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Our cells respond to invading DNAs formed by viral infection in a variety of ways to suppress their ability to produce RNAs and proteins. One mechanism is to wrap the DNA with histones into a form of chromatin – so-called heterochromatin – that is highly condensed and inaccessible to machinery needed for viral gene expression. Furthermore these histones are covalently modified with specific marks that are associated with silent chromatin – deacetylation of histones, and trimethylation of lysine 9 on histone 3 (H3K9me3). The viral DNA formed by HIV-1 early in infection, before the DNA is integrated into the host genome, is an example of an incoming DNA subject to this profound silencing. In this paper, tests for the host genes that might be required for silencing identified two chromatin modifiers, CHAF1A and B, as important players (Geis et al, 2022). CHAF1A (chromatin assembly factor 1 subunit A), and CHAF1B (chromatin assembly factor 1 subunit B) are components of the evolutionarily highly conserved CAF-1 (chromatin assembly factor 1) complex responsible for canonical H3 deposition. Knockdown (KD) of expression of either of these two proteins resulted in dramatic loss of silencing of reporter genes delivered by integration-deficient HIV-1 viral vectors. We examined the loading of histones by Chromatin ImmunoPrecipitation (ChIP) and qPCR assays of viral DNAs. We noted high levels of the variant histone H3.3, and also the linker histone H1, typically associated with condensed heterochromatin, present on the viral DNA. There was no change with CHAF1A/B KD in the loading of histones per se, but a significant reduction in the levels of the H3K9me3 modification. The loss of this silencing mark may account for at least a portion of the relief of silencing. To test for the generality of the role of CHAF1A and B in silencing incoming viral DNA, we performed similar tests with reporter genes delivered by integration-defective murine leukemia virus (MLV) vectors. Reporter genes on MLV genomes, like those on HIV-1 genomes, are also profoundly silenced. Remarkably, in contrast with the results with the silencing of HIV-1, the KD of CHAF1A and B had no effect on the silencing of MLV gene expression. Thus, we conclude that various viral DNAs are silenced by distinct sets of host proteins. A more complete understanding of the silencing machinery will suggest new therapeutic opportunities to control viral gene expression early in infection, and to reduce the efficiency of transmission of virus and perhaps the establishment of viral latency.

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## Publication

CHAF1A/B mediate silencing of unintegrated HIV-1 DNAs early in infection
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